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EDITORIAL

# Are we closer to having drugs to treat muscle wasting disease?

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**Abstract** The two most common muscle wasting diseases in adults are sarcopenia and cachexia. Despite differences in their pathophysiology, it is believed that both conditions are likely to respond to drugs that increase muscle mass and muscle strength. The current gold standard in this regard is exercise training. This article provides an overview of candidate drugs to treat muscle wasting disease that are available or in development. Drugs highlighted here include ghrelin agonists, selective androgen receptor molecules, megestrol acetate, activin receptor antagonists, espindolol, and fast skeletal muscle troponin inhibitors.

In adults, the two most common muscle wasting diseases are sarcopenia and cachexia [1, 2]. Both conditions are major causes of frailty in older persons [3]. Sarcopenia has now been defined by multiple organizations to be a loss of function, defined by walking speed or distance coupled with a loss of muscle mass [4–6]. The clinical utility of this definition has been validated [7–9]. Sarcopenia differs from cachexia in that histologically, it predominately represents a condition primarily due to neurodegeneration coupled with a variety of other factors [10]. In contrast, cachexia is an inflammatory muscle disorder, which is associated with loss of adipose tissue and anorexia [11–13]. Despite these differences, it is believed that both conditions are likely to respond to drugs that increase muscle mass and muscle strength.

At present, the gold standard for increasing muscle function is exercise [14, 15]. Following hip fracture high-intensity progressive resistance training decreased mortality and nursing home admissions [16]. In lung cancer, exercise increased the 6 m walk by over 50 m [17]. Exercise in cachexia can reduce inflammation, decrease reactive oxygen species, increase protein synthesis, and decrease protein catabolism [18]. In sarcopenia, while the major effects of exercise appear to be enhancing protein metabolism, there is also evidence that it may improve motor unit function [19]. Exercise also stimulates non-satellite stem cells in skeletal muscle which release growth factors resulting in muscle satellite cell proliferation and differentiation [20].

There is increasing evidence that protein supplementation acts to increase muscle synthesis and that this effect is enhanced in conjunction with exercise [21]. The PROTAGE consensus has supported the need for 1 to 1.5 g/kg of high-quality protein (leucine-enriched, balanced essential amino acids) to restore muscle in persons with sarcopenia [22].

The Cochrane collaboration has shown that in malnourished older persons, protein and energy supplementation produces weight gain and reduces mortality [23]. The INTERCOM trial showed that 24 months of nutritional intervention, coupled with exercise in chronic obstructive pulmonary disease, enhanced muscle strength and 6 min walk distance and decreased hospitalization [24]. Caloric supplementation in persons with heart failure enhanced weight and improved quality of life [25]. Nutritional support following hospitalization in malnourished older persons improves functional limitations [26]. In this editorial, we will review the recent advances in drug therapy for sarcopenia and cachexia as presented at the seventh International Cachexia Conference

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in Kobe, Japan in December 2013, and place these findings into perspective.

New data on two orexigenics was presented. Of these, ghrelin-like agents represented a major component of the meeting. Ghrelin is produced in the fundus of the stomach and enhances food intake, growth hormone secretion, and muscle mass gain. Its effect on feeding is produced through enhancing nitric oxide synthase activity [27]. It has been shown to increase food intake and stop muscle mass loss in cancer [28]. It has similar positive effects following esophagectomy [29]. Other studies have shown that the ghrelin agonist, capromelin, increased lean mass, tandem walk, and stair climb over 12 months in older sarcopenic individuals [30]. MK-0677, a potent growth hormone-secretagogue mimetic, which works through the ghrelin receptor, improved stair climb and decreased falls in a 24-week study in patients who had had hip fracture [31]. There was, however, an increase in heart failure in the treated group. At the conference, the phase II results of the ghrelin agonist, anamorelin, were presented [32]. Overall, it enhanced body weight, tended to improve handgrip strength, increased appetite and quality of life, and decreased inflammatory markers (C-reactive protein, interleukin-6, and tumor necrosis factor).

Further data on an immunomodulatory, orexigenic drug OHR118 was presented confirming its positive effects on appetite and weight stabilization in a non-placebo-controlled trial [33, 34]. There was no new data on megestrol acetate, a mixed progestagen/testosterone/corticosteroid agent, which increases food intake and weight gain (predominantly fat) in cancer and AIDS [35] and older persons [36]. A combination of megestrol acetate plus thalidomide improved weight gain, quality of life, and grip strength [37]. Megestrol also improved weight in children with cancer [38]. Megestrol is barely absorbed if taken without food, and this can be overcome by using a nanocrystal form [39]. Cannabinoid-like drugs produce less of an increase in food intake and weight gain than megestrol [40]. There is no data available on the effects on appetite and weight gain of the cannabinoid oromucosal spray [41]. While cannabinoids may be excellent drugs for hospice care, it is unlikely that they will prove to be useful orexigenic drugs [42].

Testosterone has been long utilized to improve muscle mass and strength and to a lesser extent function in older persons with sarcopenia [43–48]. It has been shown to improve walking distance in persons with heart failure [49, 50]. In combination with a caloric supplement, testosterone markedly decreased hospitalization in frail older persons living in assisted living [51]. Uncertainty of the side effects associated with testosterone therapy has led to the development of selective androgen receptor molecules (SARMs). Enobosarm has been shown to improve lean body mass and stair climb in older men and women [51, 52]. In patients with cancer, enobosarm increased lean mass [53]. At the Cachexia meeting, new data demonstrated that enobosarm improved stair climb in one out of two cancer chemotherapy studies [54]. Their data suggested that in the cancer patients who maintained lean body mass, there was an improvement in survival.

The activin receptor plays a major role through which myostatin inhibits muscle growth [55]. A number of myostatin antibodies have been developed, which at present have not been shown to have a significant effect on muscle gain in humans [56, 57]. Decoy activin II receptors increase lean body mass and bone mineral density [56, 58]. Unfortunately, bleeding associated with this agent appears to limit its usefulness. Inclusion body myositis is a rare autoimmune disease associated with amyloid inclusion bodies that occurs in persons over 50 years of age [59].

Bimagrumab is an activin II receptor antibody. A preliminary study, presented at the seventh International Cachexia Conference, suggests that over a 24-week period, it increased lean body mass, quadriceps strength, and physical performance in persons with sporadic inclusion body myositis [60].

Two cardiological drugs classes have been shown to have effects on muscle function. Perindopril, an angiotensin-converting-enzyme inhibitor, improves distance walked in older persons and in persons with heart failure [61, 62]. Perindopril was used in the Hypertension in the Very Elderly (HYVET) study in which there was a decrease in hip fracture, despite the other agent being a diuretic [63]. Espindolol is a non-specific $\beta_1/\beta_2$ adrenergic receptor antagonist which has been shown to improve lean mass in rats [64]. In a randomized, double-blind placebo-controlled phase II study in patients with lung or colorectal cancer, espindolol reversed body weight loss seen in the placebo group and maintained lean body and fat mass [65]. It also increased hand grip strength. Trends for functional improvement were also observed.

A new class of drugs is fast skeletal muscle troponin activators (tirasemtiv and CK-2127107). These drugs amplify the response to motor neuron input, increase muscle power, and improve muscle fatigability. Preliminary data has suggested that tirasemtiv may improve function in persons with amyotrophic lateral sclerosis (ALS) [66]. A phase III study in amyotrophic lateral sclerosis is now ongoing. Phase I studies for CK-2127107 have shown it to be safe.

Finally, studies enhancing mitochondrial function by increasing NAD [67] or enhancing Cisd2 function of the outer mitochondrial membrane [68, 69] can enhance muscle function. Bendavia, a novel mitochondria-targeting peptide, restored skeletal muscle fiber type in dogs with heart failure [70].

Since the initiation of the Journal of Cachexia, Sarcopenia, and Muscle in 2010 [71], there has been a remarkable increase in our knowledge regarding the treatment of muscle wasting diseases. It would seem, based on the therapeutic approaches, it is now time to move from using names such as myopenia,

sarcopenia, or cachexia to characterize these disorders [72] and to characterize these conditions under the umbrella of "muscle wasting diseases" [73].

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